Very Mild PeRioperative HypOThErmia *versus* Aggressive Warming and myoCardial injury afTer non-cardiac surgery (PROTECT)

February 01, 2021

NCT03111875

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Abstract

Myocardial injury is the most common cause of death in the 30 days after non-cardiac surgery. Hypothermia increases sympathetic activation, promotes tachycardia, and causes hypertension — all of which may increase the risk of myocardial injury. Only one small study evaluated the relationship between moderate hypothermia and myocardial infarction, and was unable to make definitive conclusions. Moderate perioperative hypothermia is now uncommon, but mild hypothermia (≈35.5°C) remains common. Whether aggressive warming to a truly normothermic level (≈37°C) improves outcomes remains unknown. We therefore propose to test the primary hypothesis that aggressive warming reduces the incidence of major cardiovascular complications. Up to 5,058 patients will be randomly assigned to routine care (core temperature ≈35.5°C) or aggressive warming (>37°C core temperature) in a multi-center trial. Patients will be randomly: 1) **routine thermal management** with rescue intraoperative forced-air warming to prevent core temperature from decreasing to less than 35.5°C; or, 2) **aggressive warming** to a target final intraoperative core temperature between 37 and 37.5°C. The **primary outcome** will be a composite of myocardial injury (troponin elevation, apparently of ischemic origin), non-fatal cardiac arrest, and all-cause mortality within 30 days of surgery. **Secondary outcomes**, also within 30 days, will include: 1) 30-day deep or organ-space surgical site infection, as defined by Center for Disease Control criteria; 2) intraoperative transfusion requirement, defined as units of red blood cells transfused; 3) duration of hospitalization; and, 4) readmission within a month of surgery.

Trial Management

Trial management will include an Executive Committee, a broader Steering Committee, and a Data and Safety Monitoring Board (DSMB) consisting of experienced trialists who have no other involvement in the study. The Steering Committee will advise the Executive Committee and Principle Investigator, as will the DSMB. Normally, the DSMB will evaluate blinded results (Group A vs. Group B) at each interim analysis, and at other intervals as they see necessary. The DSMB may request unblinded results if there is a safety concern.

Executive Committee

Daniel I. Sessler
Andrea Kurz
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Steering Committee

Member of the Executive Committee	
Yuguang Huang	PUMCH, Beijing
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Jingxiang Wu	Shanghai Chest Hospital, Shanghai
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Jens-Ulrik Staehr Jensen, MD Assoc Prof & Head of Resp Med Herlev-Genntofte Hospital University of Copenhagen Copenhagen, Denmark	Anupa Wadhwa, MD Professor of Anesthesiology University of California San Diego, California
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Background

In recent decades, intraoperative mortality has decreased by a factor-of-ten, even though we now care for much sicker and older patients.[1] Preventable anesthetic-related intraoperative mortality is now so rare that it is hard to quantify.[2] Postoperative mortality, in contrast, remains substantial. Overall 30-day postoperative mortality is about 1% in the United States, and about 2% amongst inpatients (outpatients die much less frequently).[3,4] To put this mortality in perspective, if the postoperative period were considered a disease, it would represent the third leading cause of death in the United States.[5] Roughly a quarter of all 30-day postoperative deaths are cardiovascular, or consequent to cardiovascular events — with myocardial injury being by far the most common.[6]

Worldwide, 8% of surgical inpatients >45 years of age have a postoperative myocardial injury as defined by a troponin elevation that is due to an ischemic etiology, with only 22% of these events fulfilling the diagnostic criteria of the universal definition of myocardial infarction.[7] Only 7% of patients experiencing a perioperative myocardial infarction will have chest pain, and 65% are entirely clinically silent which means that they will go undetected without routine troponin screening.[6-9]

It is tempting to dismiss asymptomatic biomarker elevation as “troponitis” and assume that it is inconsequential; however, this would be a mistake because 30-day mortality in patients with elevated postoperative troponin is significantly and substantially increased *with and without* symptoms.[10] The term Myocardial Injury after Non-cardiac Surgery (MINS) recognizes that troponin elevations without a non-ischemic explanation (e.g., sepsis, pulmonary embolus) are clinically important — even in patients whose symptoms and signs do not meet the formal definition of a myocardial infarction.[11]

Mortality at 30 days in patients with MINS is a concerning 10%, which represents a five-fold increase from background risk. Mortality increases exponentially as a function of peak postoperative troponin concentration, ranging from 9% for fourth-generation troponin T plasma concentrations of 0.03-0.29 ng/ml to 17% for concentrations $\geq$0.3 ng/ml. Moreover, it is not just mortality that is increased: a composite of nonfatal cardiac arrest, congestive heart failure, stroke, and death occurred at a rate of 2.4% in patients without MINS and 18.8% amongst those with MINS, a factor-of-eight increase.[10] The corresponding thresholds for generation five, high-sensitivity troponin T are ≥20 ng/L with at least a 5 ng/L increase from baseline, or troponin ≥65 ng/L with or without an increase from baseline. When postoperative troponin concentrations are between 65 and 1,000 ng/L, mortality is increased 70-fold.[7]

It is thus reasonable to ask what perioperative factors might contribute to MINS. Among the likely candidates is hypothermia. Moderate perioperative hypothermia (e.g., 34.5°C) has been shown to cause surgical site infection,[12] coagulopathy,[13] reduced drug metabolism,[14-16] prolonged postoperative recovery,[17] and thermal discomfort.[18] Thermoregulatory vasoconstriction, a response to hypothermia, increases systemic vascular resistance and consequently causes hypertension.[19] When combined with thermal discomfort and shivering, hypothermia also causes tachycardia.

Among the major complications of hypothermia, myocardial outcomes are least well established. A recent observational analysis suggests an association between SCIP-10 compliance on temperature and cardiovascular outcomes.[20] A single-center randomized trial of 300 patients evaluated cardiac outcomes, and the study was seriously under-powered.[21] For example, only two hypothermic patients had a cardiac arrest and one had a myocardial infarction *versus* none in the normothermic group (36.7°C). Ten hypothermic patients experienced cardiovascular events *versus* two in normothermic patients. These fragile results, based on fewer than ten outcome events, are nearly as likely to be wrong as right,[22] and a poor basis for health policy. The other relevant study had only 100 patients and was thus even more fragile.[23]

An additional limitation of Frank *et al*[21] is that diagnosis was primarily based on Holter ECG finding rather than troponin concentrations which are much more sensitive. Consequently, the overall myocardial infarction rate was <1% where the true rate is no less than 10% in vascular surgery patients. It is highly questionable whether any conclusion about hypothermia and myocardial outcomes can be derived from a study that missed 90% of the presumed myocardial events. The only other relevant trial was restricted to just 100 patients leaving it even less powered to detect clinically important outcomes.[23] There thus remains considerable doubt as to the true effect of moderate hypothermia on cardiovascular outcomes.

An additional issue is that perioperative normothermia is often defined as a core temperature ≥36°C. The difficulty is that 36°C is *never* a normal temperature in humans. Even at the circadian nadir, usually about 3:00 AM, core temperature is not normally below 36.5°C; and at about 3:00 PM, core temperature is typically about 37.5°C.[24] On average, then, normal body temperature in humans is about 37°C, not the 36°C that is widely accepted as suitable for perioperative patients.[20,25]

At any given time of day, core temperature is actively controlled by the thermoregulatory system.[26] In other words, circadian temperature changes are not passive responses to environmental perturbations — which suggests that humans function best at temperature near 37°C. Consistent with this theory, randomized trials have shown that mild perioperative hypothermia causes coagulapathy,[13,27] increased blood transfusion,[13,27] surgical site infection,[12] delayed drug metabolism,[15,16,28] prolonged recovery,[17] and prolongs the duration of hospitalization.[12]

We therefore propose to test the hypothesis that aggressive warming to >37°C core temperature, versus typical thermal management (≈35.5°C) prevents major adverse cardiac events, defined as 30-day myocardial injury (troponin elevation), non-fatal cardiac arrest, and all-cause mortality. Secondary outcomes will include infection, transfusion, duration of hospitalization, and hospital re-admission within 30 days.

Methods

This will be a multicenter, international, randomized clinical trial. The trial will be coordinated by the department of OUTCOMES RESEARCH in Cleveland Clinic, Ohio, USA. About 200 people will be enrolled at the Cleveland Clinic. About 5,058 patients will participate at about ten Chinese hospitals.

Inclusion Criteria

Consenting patients will be eligible if they are:

1. Scheduled for major noncardiac surgery expected to last 2-6 hours;
2. Having general anesthesia;
3. Expected to require at least overnight hospitalization;
4. Expected to have >50% of the anterior skin surface available for warming;
5. Age over 45 years;
6. Have at least one of the following risk factors:
    a. Age over 65 years;
    b. History of peripheral arterial surgery;
    c. History of coronary artery disease;
    d. History of stroke or transient ischemic attack;
    e. Serum creatinine >175 μmal/L (>2.0 mg/dl);
    f. Diabetes requiring medication;
    g. Hypertension requiring medication;
    h. Current smoking.

Exclusion Criteria

Patients will be ineligible if they:

1. Have a clinically important coagulopathy in the judgement of the attending anesthesiologist;
2. Are septic (clinical diagnosis by the attending anesthesiologist);
3. Body mass index exceeding 30 kg/m^2;
4. End-stage renal disease requiring dialysis;
5. Surgeon believes patient to be at particular infection risk.

Protocol

Patients will be randomized 1:1, stratified by site, with random-sized blocks. Investigators will access a web-based site about an hour before surgery is expected to start, after consent is obtained. Allocation will thus remain concealed until the last practical moment.

The treatments will be: 1) **routine thermal management** with rescue intraoperative forced-air warming to prevent core temperature from decreasing to less than 35.5°C; or, 2) **aggressive warming** to a target intraoperative core temperature ≥37°C. Patients will not be told to which group they are assigned.

Patients assigned to routine thermal management will not be pre-warmed and ambient intraoperative temperature will be maintained near 20°C per routine. Only transfused blood will be warmed. An upper- or lower-body forced-air cover will be positioned over an appropriate non-operative site, but will not initially be activated. Should core temperature decrease to 35.5°C, the warmer will be activated as necessary to prevent core temperature from decreasing further.

Patients assigned to aggressive warming will be pre-warmed with a full-body forced-air cover for ≈30 minutes before induction of anesthesia. The warmer will initially be set to "high" which corresponds to ≈43°C. It will subsequently adjusted to make patients feel warm, but not uncomfortably so. Patients will be aggressively warmed during surgery to a target intraoperative core temperature between 37 and 37.5°C, using two forced-air covers when clinically practical. All intravenous fluids will be warmed to body temperature. There is no need to control ambient temperature since ambient temperature has little effect on core temperature in patients warmed with forced air (Pei, et al. unpublished).

In nearly all countries except the United States, this approach can be considered a randomization to routine care *versus* extra warming.[29] Numerous randomized trials demonstrate that pre-warming ameliorates redistribution hypothermia[30-36] which is otherwise the major cause of hypothermia during the initial hour of general[37] or neuraxial[38] anesthesia. About 30 minutes of pre-warming is needed for a clinically important benefit.[39] Fluid warming does not warm patients, but infusion of unwarmed fluids decreases body heat content and core temperature.[40]

Measurements

Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Cardiovascular risks will be recorded, including hypertension requiring treatment, diabetes requiring oral medications or insulin, end-stage renal disease requiring dialysis, history of previous myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, and smoking status. Cardiovascular medications will be similarly recorded, including beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins.

Type of surgery will be characterized as orthopedic, laparoscopic, open abdominal, neurosurgical (including spine), and other. Timing will be characterized as elective, urgent, or emergent. To characterize the risk of surgical site infection, we will record whether the operation involved colon resection, rectal resection, other abdominal surgery, and whether the wound was contaminated or dirty-infected.

Intraoperative core temperature will be measured in the distal esophagus, nasopharynx (10-20 cm past the nares), or pulmonary artery. Temperature will be recorded at 15-minute intervals throughout surgery. Mean-arterial pressure and heart rate will also be recorded at 15-minute intervals throughout surgery. Mean arterial pressure and heart rate will also be recorded at 15-minute intervals for the initial postoperative hour.

It will be impossible to blind patients to prewarming and intraoperative clinicians and investigators to group assignment. However, all postoperative measurements will be made by investigators who are unaware of patients' group assignment and intraoperative management. The study will thus be *assessor blinded*. To maintain blinding, the anesthesia record will be sealed in an opaque envelope before patients leave the post-anesthesia care unit. The envelope will be marked "Do not open until [date 35 days after surgery]." Some hospitals will have electronic records; in those cases, we will ask investigators evaluating postoperative outcomes not to access the anesthesia record.

Blood for generation 4 or 5 troponin T, or troponin I(per clinical routine) will be recorded preoperatively up to 2 weeks prior to day of surgery, and on the first two postoperative days so long as patients remain hospitalized.[7] Troponin samples will also be obtained if patients have shortness of breath or experience chest, neck, or arm pain. Blood troponin concentrations exceeding site thresholds (depending on individual types of troponin tests) should prompt cardiology consultation, an electrocardiogram, and if possible, and echocardiogram. Hemoglobin will also be obtained on the first postoperative morning. Other preoperative laboratory values and relevant testing will be recorded if available (but are not required per protocol), including hemoglobin, creatinine, and blood troponin concentrations after the mandated initial two postoperative days.

Quality-of-recovery 15 will be assessed on the third postoperative day in person or by phone in patients already discharged.[41] A Chinese version of the Quality-of-recovery instrument has been validated.[42] If discharged patients cannot be reached on the third postoperative day, attempts will be made on the fourth postoperative day. Patients will also be evaluated for various outcomes on the day of hospital discharge and 30 days after surgery, with a +5-day window. That is, attempts to contact patients will begin about day 30 and continue through postoperative day 35. The study will be censored at day 30, even if patients remain hospitalized.

The **primary outcome** will be a composite of myocardial injury after non-cardiac surgery (MINS), non-fatal cardiac arrest, and all-cause mortality within 30 days of surgery. Myocardial injury will be diagnosed by objective screening based on preoperative and first two postoperative day troponin values crossing site specific thresholds for MINS so long as patients remain hospitalized. Abnormal troponin concentrations will be evaluated as clinically indicated with ECG, echocardiography, and clinical symptoms; the resulting values will be recorded, as will other cardiovascular interventions such as angioplasty. MINS will be diagnosed by troponin exceeding individual sites thresholds apparently of ischemic origin (e.g., no other obvious cause for artifactual elevation). Myocardial infarction will also be centrally adjudicated and require *both* MINS and at least one symptom (e.g., chest pain or shortness of breath) or sign (e.g. ECG or echocardiogram abnormality).

We will consider all patients who had an elevated serum troponin concentration anytime during the first 30 days after surgery and determine the presence of any ischemic features (*i.e.*, whether patients fulfilled the universal definition of myocardial infarction),[43] whether there was a non-ischemic etiology that could explain the elevated troponin

measurement, and whether the myocardial injury appears to have occurred during or after surgery (*i.e.*, no evidence to support it was due to a preoperative event).

Myocardial injury will be considered when a postoperative troponin concentration is elevated and believed to be consequent to myocardial ischemia. The thresholds differ depending on the assay generation and type. We will use the following thresholds based on available literature:

1. non-high-sensitivity (fourth-generation) troponin T ≥0.03 ng/ml;
2. high-sensitivity troponin T ≥65 ng/L; or high-sensitivity troponin T 20-64 ng/L and an increase ≥5 ng/L from baseline;
3. high-sensitivity troponin I (Abbott assay) is ≥75 ng/L[44];
4. high-sensitivity troponin I (Siemens assay) is ≥60 ng/L (Borges, unpublished);
5. troponin I (other assays) is at least twice local 99th percentiles;
6. an increase of at least 20% in patients who have *preoperative* high-sensitivity troponin concentrations that exceed 80% of the relevant thresholds in items 2-5.

For patients with a chronic elevation or an acute myocardial injury before surgery, a new myocardial injury after surgery requires identification of a new elevated troponin after surgery as per points 1-5 above, and the troponin elevation must be a 20% rise beyond the chronic troponin value or beyond the last measurement of the acute preoperative myocardial injury that was clearly demonstrated to have peaked and was coming down. Patients meeting diagnostic criteria for MINS will be evaluated for myocardial infarction with EKG and ECHO with cardiac consultation, which will help us detect all infarctions and increase the baseline incidence.

Secondary outcomes will include:

1) 30-day deep or organ-space surgical site infection, as defined by Center for Disease Control criteria*;
2) Intraoperative transfusion requirement, defined as units of red blood cells transfused;
3) Duration of hospitalization (censored at 30 days);
4) Readmission within a month of surgery;

Exploratory outcomes will be:

1) Estimated intraoperative blood loss;
2) The change in blood hemoglobin from preoperatively to the first postoperative morning;
3) 30-day superficial surgical site infection;
4) Quality-of-recovery 15 on the third postoperative day in person or by phone in patients already discharged;[41]
5) 30-day myocardial infarction meeting requirements of the Third Universal Definition.[43]

*Definitions of surgical site infections, modified from 1990 CDC criteria: http://www.cdc.gov/hicpac/SSI/table1-SSI.html.

1. **Superficial infection**

Infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:

- Purulent drainage from the superficial incision.
- Organisms isolated from culture of fluid or tissue from the superficial incision.
- At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative.
- Diagnosis of superficial incisional SSI by the surgeon or attending physician.

2. **Deep infection**
Infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision *and* at least *one* of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
- A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
- Diagnosis of a deep incisional SSI by a surgeon or attending physician.

3. **Organ-space infection**
Infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation, *and* at least *one* of the following:

- Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space.
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
- Diagnosis of an organ/space SSI by a surgeon or attending physician.

Outcomes will be centrally adjudicated by investigators blinded to randomization and intraoperative core temperatures.

Data will be recorded on case-report forms and directly entered via a web site into a secure REDCap database (i.e., with a tablet computer). All HIPAA rules will be followed; no identified data from remote sites will be entered into REDCap, and no Clinic data will be sent elsewhere. We will request a copy of the anesthesia record, redacted for

protected health information, for auditing purposes. Similarly, we will request redacted copies of key lab tests and records related to defined outcomes.

Statistical Plan

Reported temperatures will include time-weighted average, minimum, and final intraoperative core temperatures.

Analyses will be modified intent-to-treat, including all randomized patients who received treatment (i.e., patients randomized but not receiving treatment will not be included in any analyses). Randomized groups will be compared on baseline and demographic characteristics using absolute standardized difference, defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation. All analyses will adjust for any imbalanced baseline characteristics between randomized groups, defined as the maximum of 0.10 and absolute standardized difference > $1.96 \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$.

Missing outcomes will be imputed using an appropriate method, after examining the missing mechanism and drop-out rates. If less than 5% of data are missing, we will assign worst outcome to the active treatment group and best outcome to the control group for patients missing all records of MINS, non-fatal cardiac arrest and mortality; we will apply the last observation carried forward (LOCF) method for patients missing 30-day follow-up data but having discharge assessment. If missing is 5~20%, we will use the multiple imputation method.

Primary analysis

We will assess the effect of warming strategy on the binary-event composite of myocardial injury, non-fatal cardiac arrest, and all-cause mortality within 30 days of surgery, using a multivariate generalized estimating equations (GEE) method.[44,45] A common effect GEE test with an unstructured working correlation matrix will be performed, assuming that each component is similarly affected by intervention. The treatment-by-component interaction will be examined in a separate distinct effects GEE model to assess the heterogeneity of the treatment effect across outcomes.

Secondly, we will estimate the average relative effect of aggressive warming across the three categories of complications, using a GEE 'distinct effects' model with an unstructured working correlation matrix. This method is not driven by component with the highest frequency but may have a lower power compared to common effects model because one complication has a lower expected incidence. Regardless of the existence of the interaction, we will report the treatment effect of aggressive warming for each complication. The significance criterion will be 0.017 for each association (i.e., 0.05/3, Bonferroni).

Secondary analyses

The effect of warming strategy on collapsed composite of 30-day deep or organ-space surgical site infection and readmission within a month of surgery will be assessed using separate chi-square tests or multivariable logistic regression models, as appropriate.

The effect of warming strategy on the intraoperative transfusion requirement, defined as units of red blood cells transfused, will be assessed using a multivariable Poisson or negative binomial regression model, as appropriate.

Finally, the effect of warming strategy on time to discharge alive will be assessed using a Cox proportional hazards regression model. Patients who died before discharge will be assigned a censoring time equal to the longest observed duration of hospitalization.

To assess the robustness of our primary analysis, we will conduct per-protocol analysis for primary outcome by analyzing the subset of patients who completed the treatment originally allocated and without missing outcome data. This analysis is expected to be biased in favor of the preferred treatment and therefore no inference will be made about results.

Exploratory analyses

Groups will be compared on estimated intraoperative blood loss; the change in blood hemoglobin from preoperatively until the first postoperative morning, adjusted for interim transfusions; and quality-of-recovery 15 on the third postoperative day. We will use multivariable linear regression models, adjusted for potential confounders. The effect of warming strategy on 30-day superficial surgical site infection and myocardial infarction will be assessed using a chi-square test or multivariable logistic regression model.

Moreover, the association between the time-weighted intraoperative core temperature and the primary outcome will be assessed using a multivariable logistics regression model, adjusted for all potential confounders.

We will use an overall alpha of 0.05 for each of the primary, secondary, and tertiary analyses. Specifically, the significance criterion is 0.05 for primary analysis, 0.0125 for each secondary analysis (i.e., 0.05/4, Bonferroni). Holm-Bonferroni correction will be used for the exploratory analysis.

Sample-size Estimate

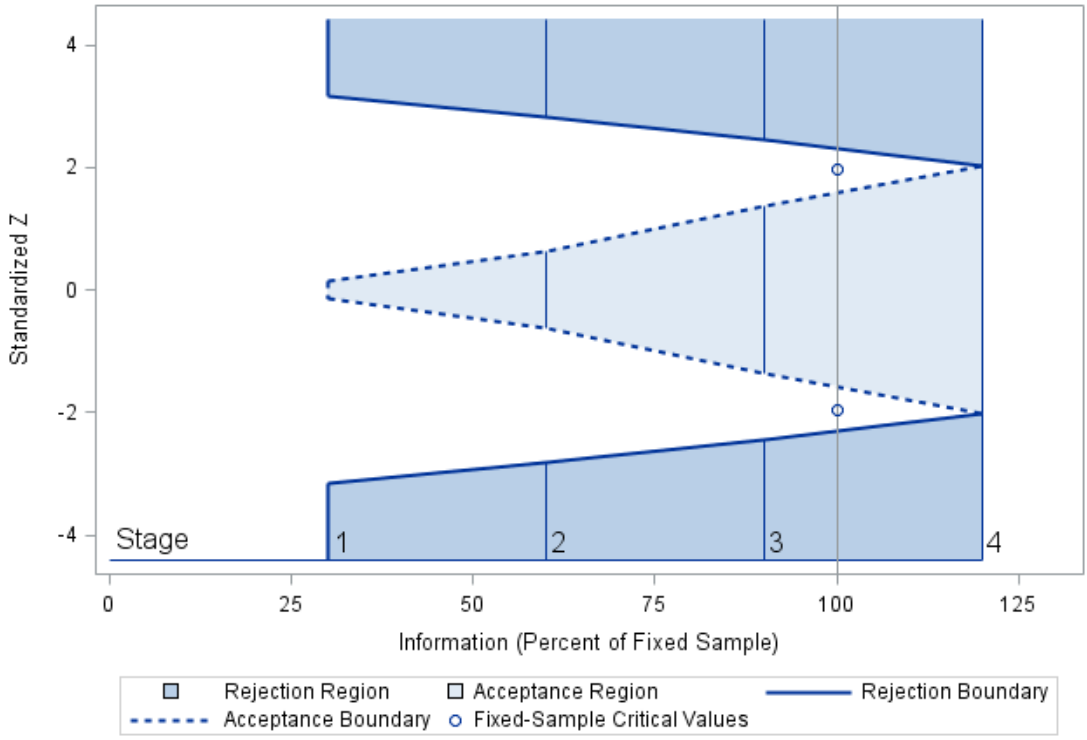
Amongst 10,000 patients enrolled in POISE-2, 8,449 met the inclusion criteria proposed for PROTECT. The incidence of MINS, nonfatal cardiac arrest, and total mortality within 30 days post-operatively were 10%, 0.1% and 1% respectively.[46,47] These studies were largely conducted outside the United States and we can thus assume that most patients were either unwarmed or inadequately warmed. We will thus assume that patients assigned to routine management will have a similar incidence of our composite outcome.

A total of 4000 patients will give a power of 0.9 at the 0.05 significance level to detect a 30% or more relative reduction in the primary outcomes, comparing routine

thermal management group to aggressive warming group. Sample size was calculated for common effect GEE model with unstructured covariance matrix, assuming a correlation of 0.1 between outcomes. We estimated sample size using the MULTBINPOW SAS macro [Mascha EJ Power Calculation for Tests on a Vector of Binary Outcomes], which can estimate the power for multivariate GEE model given varying correlation and sample size.

After accounting for interim analysis at each 25% of the maximum enrollment (3 interim analyses and a final analysis, as needed), a maximum of 4802 patients would be needed (2401 per group) for the analysis**.**

For the primary analysis, we will use a group sequential design with a nonbinding beta boundary, employing a gamma spending function with parameter gamma of -4 for efficacy and 0 for futility, thus spending beta (for futility monitoring) considerably faster than alpha (for efficacy monitoring). Boundaries for efficacy (futility in parentheses) at the each interim and final analyses are $P \leq 0.001$ ($P > 0.880$), $P \leq 0.005$ ($P > 0.525$), $P \leq 0.014$ ($P > 0.169$), and $P \leq 0.044$ ($P > 0.044$), respectively, based on an anticipated 30% treatment effect. Figure 1 shows the z-statistic boundaries for efficacy and futility at each interim look.



Stage	Boundary Values			
	Lower		Upper	
	Alpha	Beta	Beta	Alpha
1	-3.16	-0.15	0.15	3.16
2	-2.82	-0.64	0.64	2.82
3	-2.44	-1.37	1.37	2.44
4	-2.01	-2.01	2.01	2.01

Figure 1. Group sequential boundaries for efficacy (bottom, dark blue), harm (top, dark blue) and futility (light blue) assuming 4 possible looks (3 interim and final). Y-axis is the standardized treatment effect (difference in proportions / standard error of difference). X-axis depicts cumulative proportion of total sample size over time. The standardized Z values corresponding to the boundaries is presenting in the table below. A sample size of 4802 in total is needed, assuming 4000 in fixed sample design, 90% power and alpha=0.05. SAS version 9.4 or higher (SAS Institute, Cary, NC, USA) and R software version 3.2.1 or higher (R Project for Statistical Computing, Vienna, Austria) will be used for the analyses.

Table 1 provides the probabilities of stopping the trial for the underlying true treatment effect. Alternative (30% risk reduction), half-way between Null and Alternative and 1.5 times the alternative effect. For example, if the alternative hypothesis were true, the cumulative probability of crossing either efficacy or futility boundary at the 1st, 2nd, 3rd and 4th looks would be 0.109, 0.437, 0.812 and 1 respectively.

Table 1. Expected Cumulative Stopping Probabilities.

Effect	Expected Stopping Stage	Stopping Probabilities			
		Stage 1	Stage 2	Stage 3	Stage 4
Null	2.48	0.121	0.526	0.872	1.000
½ Null, Alt	2.89	0.093	0.345	0.675	1.000
Alternative	2.64	0.109	0.437	0.812	1.000
Alt X 1.5	1.86	0.315	0.836	0.988	1.000

In addition to the planned 4,802 patients, we will enroll an additional 250 patients to accounting for an expected maximum 5% dropout rate (lost to follow-up and failure to receive any treatment). Therefore, we anticipate to enroll a maximum of **5,052 patients in total.** We also plan six pilot patients at each study site to confirm feasibility before beginning to randomize subjects.

Adaptive Design Option

Since assumptions of primary outcome incidence and effect size our only estimates, we consider an adaptive design with the possibility of increasing the sample size in case the risk reduction is small. Our adaptive method for modifying the sequential design is based on the principle that we can protect the overall type I error rate by preserving conditional rejection probability of the remaining portion of the trial.[48] The new sample size of adaptive extension design will be calculated by formulae shown in Gao *et al*,[49] to raise the estimate of conditional power from its current value to a new target. Hypothesis testing will be done by comparing the final *Z* statistics to a new critical value satisfies conditional rejection probability principle.

Specifically, we will consider an adaptive extension at the third interim analysis (n=3,601) with no early stopping either for efficacy or futility. The conditional power will be calculated from accruing data and pre-planned sample size. If the conditional power is within a promising zone from 0.4 to 0.8, we will plan for increasing the sample size to repower the trial. The smallest treatment effect we would consider in the adaptive design is 15% reduction in the composite outcome. The effect size from the accrued unblinding data will be used for planning adaptive design. The magnitude of the sample size increase will be determined by requiring the target conditional power to be 0.9, subject to a cap of 10,000 randomized patients.

For statistical inference on adaptive group sequential design, we will implement the method described in Gao and colleagues.[50] By transforming the event obtained in the adaptive trial into an equivalent event that might have been obtained in the original trial without adaptation, we can compute the overall p-value, the confidence interval and the median-unbiased point estimate for the treatment effect, combining the results from all stages (pre and post adaptation). If the adaptation is followed by a single stage analysis,

the confidence interval and the median unbiased point estimate are available in closed form. Otherwise, the R package AGSDest *[Niklas Hack and Werner Brannath, 2015]* will be used for the analysis.

Decisions on an adaptive extension of the trial will be done in conjunction with the statistician(s) and the study executive committee, and without unblinding site investigators as to the actual treatment effect observed on the intervention for which the extension is planned. If, for product or budgetary reasons, sponsor participation is required in the adaptive decision-making, then a sponsor member may participate in the study executive committee discussion of the adaptive design under the condition that specifics of interim results would not be shared with the rest of the sponsoring institution(s) or anyone outside of the deliberating group. Trial results for an intervention for which there is an adaptive extension will not be made public or published in any fashion until the adaptive portion of the study is also complete.

Significance

Hypothermia has been proposed as a cause of morbid myocardial outcomes. But whether very mild hypothermia (i.e., 0.5°C) provokes myocardial complications has yet to be convincingly demonstrated because both existing studies are seriously under-powered, with fragile results based on fewer than ten outcome events. The proposed large trial will determine whether the results of the single existing under-powered trial are valid.

Mild hypothermia remains common in nearly every country except the United States. Unwarmed patients having major surgery typically have final core intraoperative temperatures near 34.5°C. Inadequately warmed surgical patients are typically near 35.5°C at the end of surgery. Even in the United States, many surgical patients have final intraoperative core temperatures near 35.5°C. More serious core hypothermia (i.e., 34.5°C) has been shown to provoke major complications, especially bleeding and surgical wound infections. Whether aggressive warming to a truly normothermic temperature (e.g., 37°C) is preferable to routine management remains unknown.

Limitations

Validity of the trial depends critically on achieving the target temperatures. There is little doubt that most unwarmed patients having major surgery will decrease to a core temperature near 35.5°C in a cool ambient environment. More challenging will be reaching a core temperature between 37 and 37.5°C by the end of surgery. Even with pre-warming, a high ambient temperature, and aggressive forced-air warming, core temperatures in some patients may not exceed 37°C by the end of surgery. Realistically, we hope to have at least 1°C difference in final intraoperative core temperature across the study population. Smaller differences are unlikely to cause outcome differences and would cause the study to fail on technical grounds.

It will be impossible to blind the preoperative and intra-operative teams to thermal management. Similarly, patients will know that they were pre-warmed, although they will not be told to which group they were assigned or what they might expect as a consequence. The primary outcome (a composite of myocardial injury, non-fatal cardiac arrest, and all-cause mortality) is objective and unlikely to be influenced by patient perception of warming. Most of the secondary outcomes are also objective or unlikely to be influenced by lack of blinding.

Human Subjects

Based on an early recommendation,[51] a final core temperature of ≥36°C is widely considered "normothermic" and has been incorporated into various guidelines. For example, the Surgical Care Improvement Project (recommendation #10) suggested a final intraoperative temperature or 36°C *and/or* use of active over-body warming whether or not core temperature reached 36°C.[20] Curiously, the American Society of Anesthesiologist does not have a standard for maintenance of core temperature. Perhaps as a consequence, many — but hardly all[52] — surgical patients are actively warmed in the United States. Warming is relatively uncommon even in other western countries.[29] In developing countries, few patients are actively warmed. For example, a 2015 cross-sectional survey of Beijing hospitals found that only 11% of surgical patients were actively warmed, and that more than a third of all patients having operations lasting at least 2 hours were hypothermic at the end of surgery.[53]

Recommendations to warm surgical patients are based on many randomized trials have shown that moderate hypothermia (≈34.5°C) causes complications relative to ≈36.5°C. For example, mild perioperative hypothermia causes surgical site infection,[12] promotes coagulopathy,[13] and prolongs postoperative recovery.[17] Among these complications, coagulopathy is by far the best documented in many individual studies and a meta-analysis.[13] As little as 1°C hypothermia detectably increases surgical blood loss. But whether smaller temperature differences matter is less obvious. The *only* study to ever demonstrate an outcome difference from just 0.5°C of hypothermia showed a slight increase in blood loss, with no significant difference in transfusion requirements.[54] Consequently, 0.5°C is widely used as the non-inferiority "delta" in trials of warming systems[55] and validations for clinical thermometers.[56] Not a single outcome study has evaluated perioperative temperatures of 37°C or greater.

There is thus little evidence to support 36°C as the optimal perioperative target temperature. A slightly lower temperature such as 35.5°C may be equally safe, or a higher temperature might be better. It would be well worth knowing if 35.5°C is safe because that temperature can often be maintained without the cost and effort of active warming — at least in patients having small operations in a warm operating room. In contrast, reliably warming patients to ≥37°C usually requires 30 minutes of pre-warming, two intraoperative forced-air warming covers, and a fluid warmer. (Intraoperative core temperature using a single intraoperative forced-air cover, the conventional approach, averages only 36°C.[57]) Thus while it is possible to warm most patients to ≥37°C, doing so

requires investing the time and cost of pre-warming, along with the cost of two intraoperative forced-air warming covers and a fluid warmer.

The added time, cost, and difficulty of maintaining intraoperative core temperature ≥37°C would be well worth investing if it reduced major complications, especially myocardial injury. But whether it does currently remains unknown. We propose to compare an inexpensive (or cost-free) approach that might be equally safe with a more expensive approach that potentially disrupts clinical routine but might reduce complications. Because the outcome of the trial is impossible to predict, there is thus full equipoise between the two temperature management strategies that we will evaluate.

Patients who meet inclusion criteria will be approached about participating by site-specific study personnel. In recognition of cultural differences between China and the United States with respect to medical decision-making[58] investigators will be encouraged to allow the patient to participate in the informed consent process to the extent that he/she wishes, and will utilize a legally authorized representative should the patient prefer family-based consent.[1]

Time Line

Study Procedure		Screening	Day of Surgery	POD 1	POD 2[e]	POD 3[e]	Discharge[c]	POD 30[d]
Informed consent		X						
Inclusion/exclusion criteria		X	X					
Labs	Hemoglobin	X[a]	X[a]	X	X[a]	X[a]		
	Creatinine	X[a]						
	Troponin	X	X[a]	X	X	X[a]		
Procedures	ECG	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
	ECHO	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
	Cardiac Catheterization		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Intraoperative Data			X					
Cardiovascular morbidity/mortality survey				X	X	X	X	X
QOR15						X[b]		
Surgical Site Infection survey							X	X

[1] Council for International Organizations of Medical Sciences (CIOMS) (2002). Commentary on Guideline 4 (Individual Informed Consent), Cultural considerations. *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* http://www.cioms.ch/frame_guidelines_nov_2002.htm.

a: If available
b: If patient is not reachable on day 3, survey can be completed on day 4
c: If patient is discharged on postoperative days 1-3, complete forms for postoperative day and discharge
d: If patient is not reachable on day 30, attempt to contact for consecutive 5 days
e: Complete if patient is still in hospital

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PROTOCOL AMMENDMENT LOG:

5/1/2017 - Based on new findings from second VISION cohort, we needed to change the PROTECT protocol. Specifically, we needed to get a preoperative troponin, but then only for two days afterwards. The preoperative troponin could be obtained any time before surgery, including in a preoperative assessment clinic or on the morning of surgery. As before, we'd like to know about any troponin measurements after the first two postoperative days, but measurements are not required after the first two days.

9/26/2017 – Generation–four Troponin T, generation–five Troponin T or Troponin I will be used to screen for MINS depending upon site preference. Threshold values for generation-five Troponin T listed as absolute change ≥5ng/L or postoperative values ≥ 65ng/L will be used to diagnose MINS.

10/12/2017 – "up to 2 weeks prior to day of surgery" added to page 9 paragraph 2. Troponin tests up to 2 weeks prior to day of surgery will be considered as pre-operative troponin.

11/02/2017 – Definition of MINS using generation five Troponin T was updated based on VISION 2 cohort study. An increase of ≥5 to a value of at least 20 ng/L would be considered as MINS and required evaluation with EKG, ECHO or Cardiac Consult.

12/03/2017 – Page 10 paragraph 2 line 1-4: Diagnostic criteria for MINS based upon generation four Troponin T, generation five Troponin T and Troponin I was rephrased for clarity. Page 10 paragraph 2 line 5-6: either EKG, ECHO or Cardiac Consultation changed to EKG and ECHO with cardiac consultation.

10/26/18 — Edward Mascha removed from the Executive Committee.

11/4/18 — Inclusion criterion changed from "peripheral vascular surgery" to "peripheral arterial surgery." Chi Cheung from Queen Mary hospital removed from the Steering Committee.

12/10/18 — Jens-Urlik Jensen substituted for Brian Ilfeld as Chair of the DSMB. Dr. Ilfeld declined after better understanding the requirements.

1/17/19 — Changed management from "**aggressive warming** to a target final intraoperative core temperature ≥37°C" to "**aggressive warming** to a target intraoperative core temperature ≥37°C."

5/27/2020 — "Bair Hugger and Bair Paws" changed to "forced-air" because 3M withdrew funding for the trial.

10/29/2020 — Because the trial is enrolling quickly and well, the Executive Committee decided to skip the third interim and analysis. That is, we plan to complete the trial without an interval assessment with the goal of shrinking the confidence intervals around whatever the findings might be. This decision was made without any access to by-group results.

02/01/2021 --- The following was deleted Page 9, second Paragraph

Myocardial injury after non-cardiac surgery will be defined as having a generation-four troponin T of ≥ 0.03 ng/ml, peak post-operative generation-five troponin T of ≥ 65ng/L, peak post-operative generation-five troponin T ≥ 20ng/L with change of ≥ 5ng/L from baseline and values exceeding local 99th percentile for troponin I.

The following was added P9

Myocardial injury will be considered when a postoperative troponin concentration is elevated and believed to be consequent to myocardial ischemia. The thresholds differ depending on the assay generation and type. We will use the following thresholds based on available literature:

1. non-high-sensitivity (fourth-generation) troponin T ≥0.03 ng/ml;
2. high-sensitivity troponin T ≥65 ng/L; or high-sensitivity troponin T 20-64 ng/L and an increase ≥5 ng/L from baseline;
3. high-sensitivity troponin I (Abbott assay) is ≥75 ng/L[44];
4. high-sensitivity troponin I (Siemens assay) is ≥60 ng/L (Borges, unpublished);
5. troponin I (other assays) is at least twice local 99th percentiles;
6. an increase of at least 20% in patients who have *preoperative* high-sensitivity troponin concentrations that exceed 80% of the relevant thresholds in items 2-5.

For patients with a chronic elevation or an acute myocardial injury before surgery, a new myocardial injury after surgery requires identification of a new elevated troponin after surgery as per points 1-5 above, and the troponin elevation must be a 20% rise beyond the chronic troponin value or beyond the last measurement of the acute preoperative myocardial injury that was clearly demonstrated to have peaked and was coming down.